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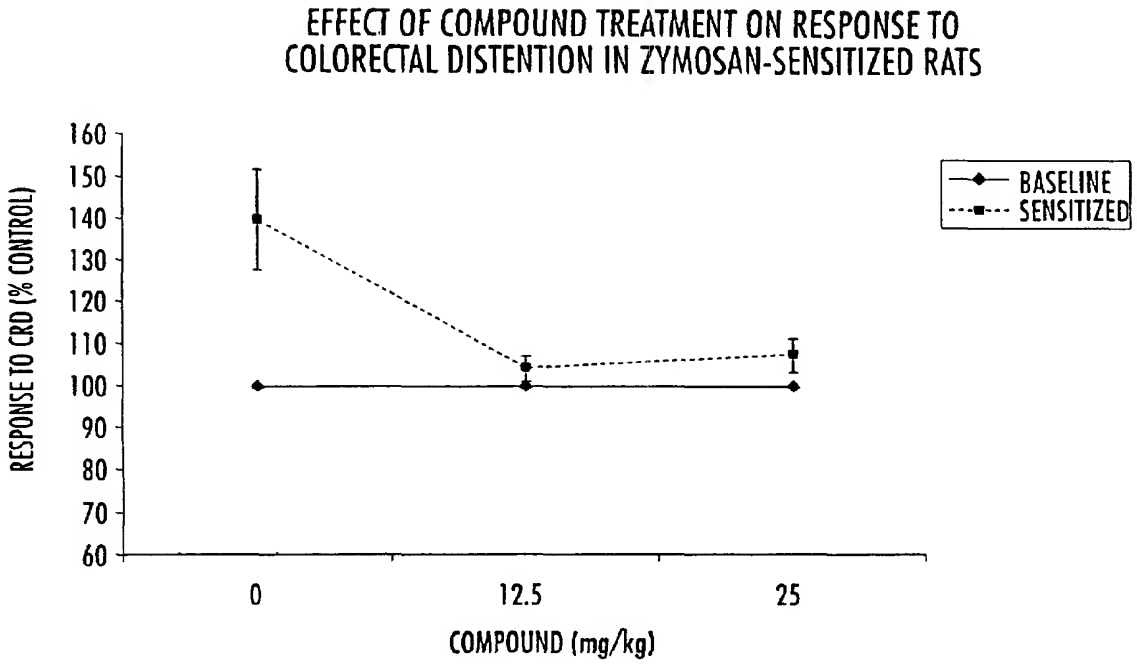
(54) Title: METHODS OF TREATING IRRITABLE BOWEL SYNDROME AND FUNCTIONAL DYSPEPSIA



(57) Abstract: The present invention relates to the use of certain glycol derivatives of xanthines for the treatment of irritable bowel syndrome and functional dyspepsia.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS OF TREATING IRRITABLE BOWEL SYNDROME AND FUNCTIONAL DYSPEPSIA

Background of the invention

The present invention relates to the use of certain glycol derivatives of xanthines, in medicine, particularly in the treatment and prophylaxis of irritable bowel syndrome and functional dispepsia.

Irritable bowel syndrome is a disease diagnosed positively by the presence of clinical features meeting the Rome criteria and by the exclusion of organic pathology justifying the symptoms. The Rome criteria for irritable bowel syndrome include continuous or recurrent symptoms of: abdominal pain or discomfort that is releived by defaecation; and/or associated with a change in frequency of stool; and/or associated with a change in consistency of stool; and two or more of the following: altered stool frequency, altered stool form, passage of mucus, and bloating or feeling of abdominal distention. IBS symptoms are reported in up to 22% of the population, with prevalence inwomen.

Certain pathophysiological mechanisms are known to lead to or aggravate irritable bowel syndrome, including abnormal motility, abnormal visceral perception, psychological distress and luminal factors irritating the small bowel or colon such as lactose, bile acids, short-chain fatty acids and food allergans.

IBS may present as diahrrea-predominant, constipation-predominant or alternating diahrrea and constipation forms.

Conventional treatments for IBS are directed toward treating the symptoms of the disease. Smooth muscle relaxant medications such as mebevarine have been employed. Alosetron, a 5HT3 antagonist, was recently approved for the treatment of diahrrea-predominant IBS.

Functional dyspepsia is a distinct type of dyspepsia. The term "dyspepsia" is defined as the general condition of indigestion and as such encompasses a variety of distinct dyspeptic conditions. There are several recognized types of dyspepsia, the most common being acid-related dyspepsia which is associated with excess gastric acidity and may lead to peptic ulcers, gastroesophageal reflux disease (GERD), and other conditions characterized by excess gastric acidity. Functional dyspepsia (FD), is not associated with excess gastric acidity. Rather, the primary pathophysiological causative factor for FD is unclear.

FD is a visceral hypersensitivity state characterized by chronic or recurrent upper abdominal symptoms in the absence of any identifiable organic pathology, such as peptic ulceration, gastric cancer, chronic pancreatitis or GERD. The absence of identifiable organic pathology is established using conventional techniques including endoscopy, radiography, histology, and other techniques known to those skilled in the art.

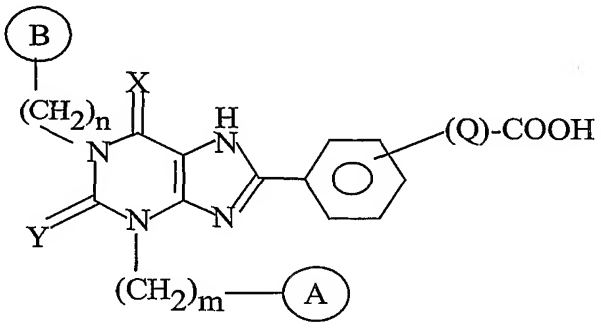
The primary symptoms of FD include upper abdominal pain or discomfort (often aggravated by food or milk or occurring after meals), early satiety (which can lead to weight loss or anorexia), nausea and vomiting, bloating, belching, and post-prandial fullness.

FD has been divided into subtypes based upon the predominant symptom(s) observed in the patient. "Ulcer-like" FD is characterized primarily by pain. "Reflux-like" FD is primarily characterized by heartburn that is often alleviated by acid-suppressing agents. It is believed that most cases of reflux-like FD can actually be attributed to GERD, and is not actually FD because the condition can be associated with an organic pathology. "Dysmotility-like" FD is characterized primarily by discomfort, bloating, nausea, vomiting, early satiety, and post-prandial fullness. "Unspecified" FD refers to FD patients having symptoms that do not fit into the above categories. Typically FD patients exhibit symptoms across the various sub-types.

The conventional treatment options for FD reflect the assumption that FD is attributable to the foregoing pathophysiological factors. The conventional treatment options for FD have proven to be of limited efficacy in many patients.

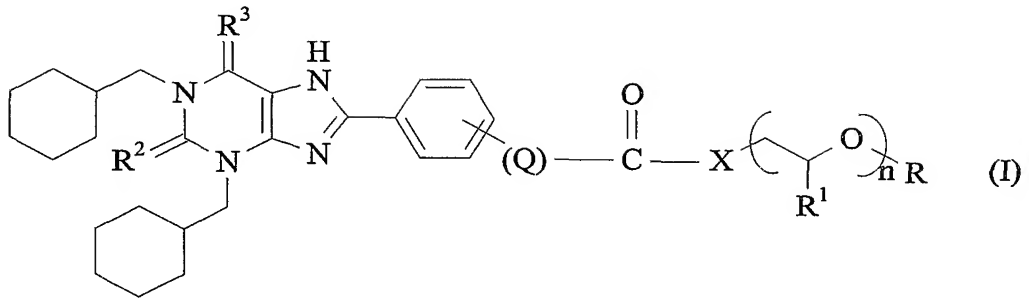
There remains a need for new methods for the treatment of IBS and FD.

PCT Publication No. WO 9604280 published 15 February 1996 to Glaxo Group Limited describes compounds of formula:



wherein m and n are independently integers from 0 to 10;
X and Y are independently oxygen or sulphur;
(-Q-) is $(-CH_2-)_p$ or $(-CH=CH-)_p$ where p is an integer of from 1 to 4; and
A and B are independently methyl, branched C_{3-6} alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;
and salts, solvates and pharmaceutically acceptable esters and amides thereof; and their use in treatment of inflammatory diseases, immune disorders, septic shock, circulatory disorders and gastrointestinal inflammation, infection or damage.

PCT Publication No. WO 98/35966, published 20 August 1998 to Glaxo Group Limited describes compounds of formula (I):



(I)

or a solvate thereof wherein:

X is -O- or -NH-;

Q is $(-CH_2-)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$ where p is an integer of from 0 to 4;

R^1 is hydrogen or methyl;

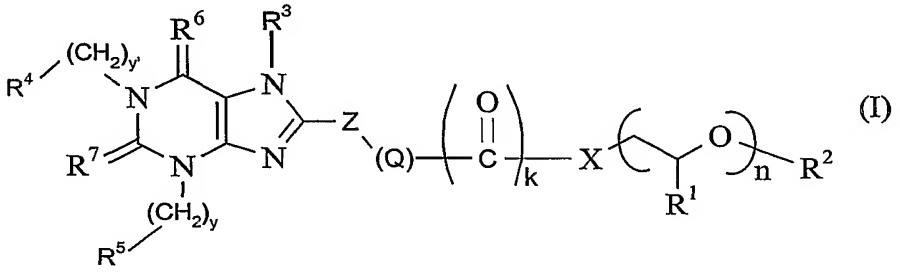
R^2 and R^3 independently represent O or S

n is an integer of 1 to 50; and

R is hydrogen or methyl;

and solvates and amides thereof; and their use in treatment of inflammatory conditions and immune disorders.

PCT Publication No. WO00/09507, published 24 February 2000 to Glaxo Group Limited describes compounds of formula (I) :



(I)

wherein

Z represents a 5 or 6 membered cycloalkyl, aryl, substituted cycloalkyl, or substituted aryl, said cycloalkyl, aryl, substituted cycloalkyl, or substituted aryl optionally containing one or more heteroatoms selected from O, N or S;

R^1 represents hydrogen or methyl;

R^2 represents hydrogen, C_{1-12}, alkyl, aryl, or aralkyl;

k represents 0 or 1

n represents an integer of 1 to 50;

X represents -O-, -N(H)-, -N(C_{1-6}alkyl)-, -N(C_{3-8}cycloalkyl)-, -N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), -N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-, $-CH_2O-$, $-CH_2NH-$, $-CH_2N(C_{1-6}alkyl)-$, $-CH_2N(C_{3-8}cycloalkyl)-$, or -$C_{1-12}$alkyl-.

m represents 0-12

Q represents $(-CH_2)_p$, (-CH=CH-)$_p$, (-C≡C-)$_p$, $(-(O)_{p1}CH2-)_p$ or $(-CH_2(O)_{p1})_p$ where

p and p^1 independently represent an integer of from 0 to 4;

y and y' independently represent integers from 0 to 10;

R^3 represents H, straight or branched C_{1-12}alkyl (optionally substituted by phenyl, -CO-phenyl, CN, -CO(C_{1-3}) alkyl, $-CO_2(C_{1-3})$alkyl, or containing one or more O atoms in the alkyl chain); C_{1-6} straight or branched alkenyl (optionally substituted by phenyl, -CO- phenyl, CN, -CO(C_{1-3}) alkyl, $-CO_2(C_{1-3})$alkyl, or containing one or more O atoms in the alkyl chain); C_{1-6} straight or branched alkynyl or a group -C_{1-3}alkyl $-NR^8R^9$

wherein R^8 and R^9 are independently H, C_{1-3}alkyl or together form a 5 or 6 membered heterocyclic group, optionally containing other heteroatoms selected from O, N or S;

R^4 and R^5 independently represent

-C_{3-8} cycloalkyl

-straight chain or branched C_{1-6}alkyl

-hydrogen

-straight or branched C_{2-6}alkenyl

-aryl or substituted aryl;

-heterocyclic group or subsituted heterocyclic group, including heteroaryl and substituted heteroaryl groups;

R^6 and R^7 independently represent O or S;

with the proviso that when

-y and y' both represent 1,

-k represents 1,

-p^1 represents zero,

-R^2 represents H or Me,

-R^3 represents H,

-X represents O or NH, and

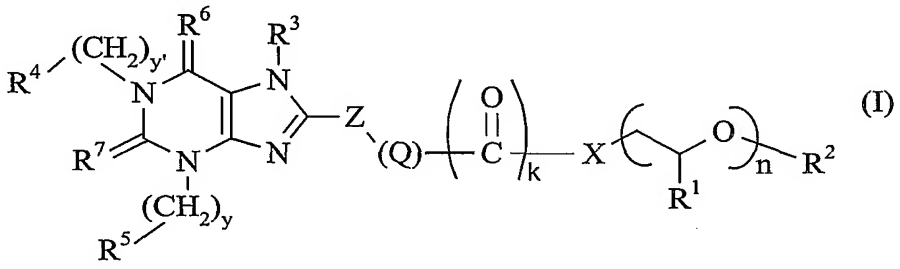
-Z represents phenyl

R^4 and R^5 do not both represent cyclohexyl;

and solvates thereof, and their use in treatment of inflammatory diseases, immune disorders, septic shock, circulatory disorders and gastrointestinal inflammation, infection or damage.

Brief Summary of the Invention

The present invention provides a method for the treatment or prophylaxis of irritable bowel syndrome in an animal, comprising administering a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

According to a second aspect, the present invention provides a method for the treatment or prophylaxis of functional dyspepsia in an animal. The method comprises administering to the animal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable solvate thereof.

According to a third aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

According to another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

According to another aspect, the present invention provides a method for the treatment or prophylaxis of irritable bowel syndrome in an animal comprising administering to the animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

According to another aspect, the present invention provides a method for the treatment or prophylaxis of functional dyspepsia in an animal comprising administering to the animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

According to another aspect, the present invention provides the use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

In yet another aspect, the present invention provides the use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

Brief Description of the Several Views of Drawings

Figure 1 is a graphical representation of the results of a study conducted in Zymosan-sensitized rats comparing the effect of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester (112.5 and 25 mg/kg) versus vehicle. Results are reported as response to colorectal distention (CRD) (as a percent of control) with increasing dosage of 0, 12.5, and 25 mg/kg of compound (sensitized --■--) as compared to baseline (--◆--).

Detailed Description of the Invention

As used herein, the term "aryl" refers to a carbocyclic group having 6-14 carbon atoms with at least one aromatic ring (e.g., phenyl or biphenyl) or multiple condensed rings in which at least one ring is aromatic, (e.g., 1, 2, 3, 4,-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl).

As used herein, the term "substituted aryl" refers to aryl as defined above optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

As used herein, the term "aralkyl" refers to a C_{1-12}alkyl that may be a straight or a branched alkyl group that is substituted by an aryl or substituted aryl group.

As used herein, the term "heterocylic group" refers to a saturated or partially unsaturated, non-aromatic group having from 5 to 12 members in a single ring (e.g. imidazolidinyl, piperidyl, piperazinyl, pyrrolidinyl, morpholinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl,

thiazylyl, thiadiazolyl, triazolyl or tetrazolyl) or multiple condensed rings (e.g. naphthpyridyl, quinoxalyl, indolizinyl or benzo[b]thienyl) and having 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, within the ring. The heterocyclic group can optionally be unsubstituted or substituted (i.e., a "substituted heterocyclic group") with e.g. halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocyclic group, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

As used herein, the term "heteroaryl" refers to a heterocyclic group as defined above in which at least one ring is aromatic.

As used herein, the term "substituted heteroaryl" refers to a heterocyclic group optionally substituted with one or more substituents including halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "membered" in reference to any of cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl refers to the total number of atoms (C, N, O and S) in the ring. Thus a 6-membered aryl is phenyl and a 6-membered heteroaryl is pyridine.

The term "alkyl" as used herein represents straight or branched hydrocarbon chains containing the indicated number of carbon atoms.

The term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and one or more double bonds, for example propenylene.

The term "cycloalkyl" includes non-aromatic carbocyclic groups containing the specified number of carbon atoms and one or more double bonds, such as cyclopropane,

cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane and includes bridged cycloalkyl groups, for example norbornyl.

As used herein, the terms "substituted alkyl" and "substituted cycloalkyl" refer to alkyl and cycloalkyl optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetroaryl, substituted heteroaryl, nitro, cyano, alkylthio, thiol, sulfamido and the like.

The term "pharmaceutically acceptable solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, or acetic acid.

In one particular aspect, the invention provides a compound of formula (I) wherein R^4 and R^5 are each independently selected from the group consisting of:
-C_{3-8}cycloalkyl;
-straight or branched C_{1-6}alkyl;
-H; and
-straight or branched C_{2-6}alkenyl.

In one embodiment, the compound of formula (I) is defined where R^4 and R^5 are each independently aryl or substituted aryl.

In another embodiment, the compound of formula (I) is defined where R^4 and R^5 are each independently selected from the group consisting of a heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl groups.

In another embodiment, the compound of formula (I) is defined where R^3 is H or C_{1-3}alkylNR^8R^9 and R^8 and R^9 are each independently H or C_{1-3}alkyl. In another embodiment, the compound of formula (I) is defined where R^3 is C_{1-3}alkylNR^8R^9 and R^8 and R^9 together with the N to which they are bonded form a 5 or 6 membered

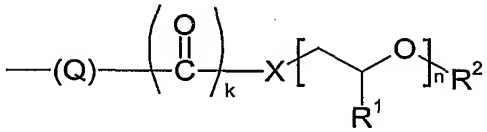
heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S.

In another embodiment, the compound of formula (I) is defined where Z is selected from the group consisting of a C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl and substituted C_6aryl.

In another embodiment, the compound of formula (I) is defined where Z is selected from the group consisting of a 5- or 6-membered heterocyclic group, substituted heterocyclic group, heteroaryl and substituted heteroaryl containing from one to three heteroatoms independently selected from O, N or S.

In one preferred embodiment, the compounds of formula (I) are defined where Z is a phenyl ring, thiophene ring or pyridine ring, more preferably phenyl.

The grouping



may be attached to Z in any suitable position. When Z is phenyl, preferably this group is attached to the phenyl ring in the para position.

In one preferred embodiment, the compounds of formula (I) are defined where R^1 is H or methyl.

In another preferred embodiment, the compounds of formula (I) are defined where R_2 is H, methyl or ethyl.

In one preferred embodiment, the compounds of formula (I) are defined where k is 1.

In one embodiment, the compounds of formula (I) are defined wherein n is 5-50. A preferred set of compounds of formula (I) are defined where n is from 8 to 20, more preferably from 8 to 15. However in certain embodiments of the present invention, such as wherein R^3 is other than H, n may preferably be shorter than 8 to 20, such as 5 to 20. Similarly, when k is 0, n may preferably be shorter than 8 to 20, such as 5-20.

Still another preferred set of compounds of formula (I) is defined where X is -O-, -N(H)-, -N(C_{1-6}alkyl)- or -N(C_{3-8}cycloalkyl)-. More preferably, X is -O-, -N(H)- or -N(CH_3)-.

In one preferred embodiment, the compounds of formula (I) are defined where Q is $(-CH_2-)_p$ or $(-CH=CH-)_p$. In one embodiment, p is 0-2, preferably 0-1. More preferably, compounds of formula (I) are defined where Q is $(-CH_2-)_p$ or $(-CH=CH-)_p$ and p is 0-4, more preferably 0-2.

One preferred set of compounds of formula (I) are defined where y and y' are the same. More preferably, compounds of formula I are defined where y and y' are both 1.

In another preferred embodiment, the compounds of formula I are defined where R_3 is methyl.

Another set of preferred compounds of formula (I) are defined where R^4 and R^5 are each independently selected from the group consisting of C_{1-6}alkyl, C_{3-8}cycloalkyl and aryl. More preferably, R^4 and R^5 are each independently selected from cyclobutyl, cyclopentyl, cyclohexyl, propyl, butyl, isopropyl, isobutyl, and phenyl. Although one preferred set of compounds is defined where R^4 and R^5 are different, another preferred set of compounds is defined where R^4 and R^5 are the same.

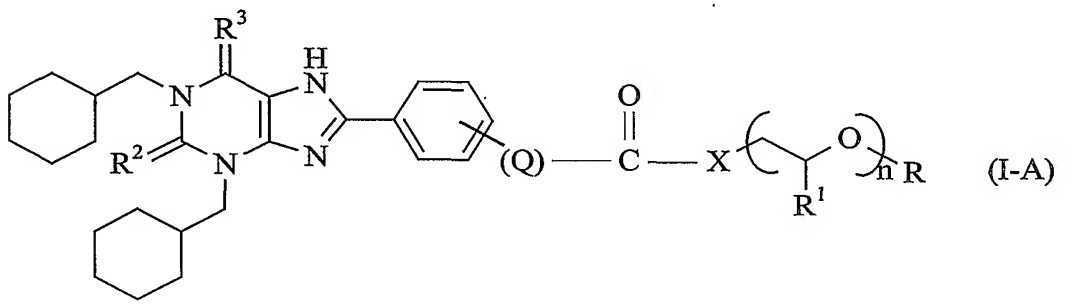
In another preferred embodiment, R^6 and R^7 are the same. More preferably, both R^6 and R^7 are 0.

According to a further aspect, the present invention provides a compound of formula (I) as defined above wherein X is -O- and R^1 is H; of these, compounds wherein n is an integer of 8 to 20 are preferred, and those wherein n is an integer of 8 to 15 are more preferred.

It is to be understood that the present invention includes all combinations and subsets of particular and preferred groups described hereinabove.

The invention also includes mixtures of compounds of formula (I) in any ratio wherein n varies.

In one embodiment, the present invention provides methods for the treatment or prophylaxis of gastrointestinal disorders, which methods comprise administering a therapeutically effective amount of a compound of formula (I-A):



(I-A)

wherein:

X is -O- or -NH-;

Q is $(-CH_2-)_p$, $(-CH=CH-)_p$ or $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

R^2 and R^3 are each independently O or S;

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

Particularly preferred compounds for use in the methods of the invention include:

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

More particularly preferred compounds for use in the methods of the present invention include:

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid-N-methyl Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

In one preferred embodiment, the present invention provides methods for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia which comprises admininstering a therapeutically effective amount of (E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester or a pharmaceutically acceptable solvate thereof.

The compounds of the present invention are capable of existing as geometric and optical isomers. All such isomers, individually and as mixtures, are included within the scope of the present invention. Where Q contains a double bond, compounds in the form of the E-geometric isomers are preferred.

Hereinafter reference to "compounds of formula (I)" shall include all compounds of formula (I), and specifically includes all compounds of formula (I-A), and pharmaceutically acceptable solvates thereof.

The compounds employed in the present invention are cell adhesion molecule inhibitors, and preferably endothelial cell adhesion molecule inhibitors. The term "cell adhesion molecule inhibitor" includes compounds which specifically block or inhibit proteins on the surface of animal cells that mediate cell-cell binding. Preferably, the term "cell adhesion molecule inhibitor" includes compounds which inhibit the expression of cell adhesion molecules.

The term "endothelial cell adhesion molecule inhibitor" includes compounds which specifically block or inhibit the adhesive interactions of leukocytes and the endothelium. These compounds can be identified by performing the endothelial cell adhesion assay as

decribed herein below. Preferably, the compounds have IC_{50} values in this assay of 500nM or less, more preferably 100nM or less and even more preferably 50nM or less. Preferably, the term "endothelial cell adhesion molecule inhibitor" includes compounds which inhibit the expression of endothelial cell adhesion molecules. More preferably, the endothelial cell adhesion molecules include ICAM-1 (Intercellular adhesion molecule-1), E-selectin, VCAM-1 and MadCAM.

The methods of the present invention involve treating or preventing irritable bowel syndrome, including diarrhea-predominant, constipation-predominant and alternating irritable bowel syndrome, and functional (non-ulcerative) dyspepsia by administering to an animal, a therapeutically effect amount of an endothelial cell adhesion molecule inhibitor, such as a compound of formula (I) or a solvate thereof. The methods of the present invention may be employed for the treatment or prophylaxis of irritable bowel syndrome and functional dyspepsia in animals generally, and particularly in mammals such as humans.

The term "therapeutically effective amount" refers to an amount of an endothelial cell adhesion molecule inhibitor, e.g., a compound of formula (I), which is effective for the treatment or prophylaxis of the stated condition. Thus, a therapeutically effective amount of a compound of formula (I) for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia is an amount effective for the treatment or prophylaxis of irritable bowel syndrome or functional dyspepsia. The term "treatment" as used herein refers to the partial or total elimination of symptoms in an afflicted animal. The term "prophylaxis as used herein refers to the complete prevention of the condition in an animal as well as the reduction in severity and/or frequency of symptoms of the condition in an afflicted animal.

The amount of an endothelial cell adhesion molecule inhibitor, e.g., a compound of formula (I) or pharmaceutically acceptable solvate thereof, which is required to achieve the desired biological effect will depend on a number of factors such as the use for which it is intended, the means of administration, and the recipient, and will ultimately be in

the discretion of the attendent physician. A typical daily dose for the treatment of irritable bowel syndrome or functional dyspepsia, for instance, may be expected to lie in the range of 0.005 mg/kg - 100mg/kg, preferably 0.5-100 mg/kg, and most preferably 0.5-20 mg/kg. This dose may be administered as a single unit dose, as several separate unit doses or as a continuous infusion. An intravenous dose may be expected to lie in the range of 0.0025 mg/kg to 200 mg/kg and would typically be administered as an infusion.

According to the methods of the present invention, it is possible to administer the compounds of formula (I) neat, although it is preferred to administer the compounds of formula (I) in the form of a pharmaceutical formulation. Thus, in a further aspect of the present invention, there are provided pharmaceutical compositions comprising, as active ingredient, a compound of formula (I) or a pharmaceutically acceptable solvate thereof, together with at least one pharmaceutically acceptable carrier or excipient. These pharmaceutical compositions may be used in the prophylaxis or treatment of irritable bowel syndrome and functional dyspepsia. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and the formulation is preferably formulated as a unit dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active ingredients. If desired other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention. In one embodiment, the methods of the present invention comprise administering a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically acceptable solvate thereof and alosetron or a pharmaceutically acceptable salt thereof.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular, or intravenous), rectal, topical including transdermal, intranasal and inhalation administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the condition being treated and on the nature of the active compound.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, lozenges, each containing a predetermined amount of the

active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically a flavoured base, such as sugar and acacia or tragacanth and pastilles comprising the active compound in an inert base, such as gelatine and glycerine or sucrose acacia.

Formulations suitable for parenteral administration typically comprise sterile aqueous solutions containing a predetermined concentration of the active compound; the solution is preferably isotonic with the blood of the intended recipient. Additional formulations suitable for parenteral administration include formulations containing physiologically suitable co-solvents and/or complexing agents such as surfactants and cyclodextrins. Oil-in-water emulsions are also suitable formulations for parenteral formulations. Although such solutions are preferably administered intravenously, they may also be administered by subcutaneous or intramuscular injection.

Formulations suitable for rectal administration are preferably provided as unit-dose suppositories comprising the active ingredient in one or more solid carriers forming the suppository base, for example, cocoa butter.

Formulations suitable for topical or intranasal application include ointments, creams, lotions, pastes, gels, sprays, aerosols and oils. Suitable carriers for such formulations include petroleum jelly, lanolin, polyethyleneglycols, alcohols, and combinations thereof. The active ingredient is typically present in such formulations at a concentration of from 0.1 to 15% w/w.

Formulations of the invention may be prepared by any suitable method, typically by uniformly and intimately admixing the active compound with liquids or finely divided solid carriers or both, in the required proportions and then, if necessary, shaping the resulting mixture into the desired shape.

For example a tablet may be prepared by compressing an intimate mixture comprising a powder or granules of the active ingredient and one or more optional ingredients, such as a binder, lubricant, inert diluent, or surface active dispersing agent, or by moulding an intimate mixture of powdered active ingredient and inert liquid diluent.

Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers, or insufflators.

Therefore, according to a further aspect of the present invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable solvate thereof in the preparation of a medicament for the prophylaxis or treatment of irritable bowel syndrome or functional dyspepsia.

Compounds of formula (I) may be prepared and formulated as described in PCT application publication Nos. WO 98.35966 and WO 00.09507, the subject matter of which is incorporated herein by reference in their entirety.

The invention will now be described by way of illustration only, by the following examples:

Cell Adhesion Assay

The antiadhesion activity of compounds described herein was determined using a modification of the previously described method, Jurgensen, C.H. et. al., *J. Immunol.* 1990, 144: 653-661. The adhesiveness of cytokine-stimulated human umbilical vein endothelial cells was assessed by quantitating the adherence of fluorescently-labelled (calcein-AM, Molecular Probes, Eugene, OR) leukocytes to endothelial cell monolayers. Activity was determined by calculating inhibition of cytokine-stimulated adhesion minus the basal adhesion (unstimulated).

Rodent Model of Zymosan-Induced Hyperalgesia

Protocol for Evaluation of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester in a Rodent Model of Zymosan-Induced Hyperalgesia

Animals

Adult male Sprague-Dawley rats (400-425 g) housed 1-2 per cage in the animal care facility at the University of Iowa (approved by the American Association for Accreditation of Laboratory Animal Care). All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Iowa.

Surgical Preparation

Rats were deeply anesthetized with pentobarbital sodium (45 mg/kg) administered intraperitoneally. Electrodes were stitched into the external oblique musculature for electromyographic (EMG) recording. Electrode leads were tunneled subcutaneously and exteriorized at the nape of the neck for future access. After surgery, rats were housed separately and allowed to recuperate for at least 3 days prior to testing.

Behavioral Testing

The descending colon and rectum were distended by pressure-controlled inflation of a 7-8-cm-long flexible latex balloon tied around a flexible tube. The balloon was lubricated , inserted into the colon via the anus, and anchored by taping the balloon catheter to the base of the tail. Noxious phasic colorectal distension (CRD, 80 mm Hg, 20 seconds) was achieved by opening a solenoid gate to a constant pressure air reservoir. Intracolonic pressure was continuously monitored by the aid of a pressure control device. Response was quantified as the visceromotor response (VMR), a contraction of the abdominal and hindlimb musculature. EMG activity produced by contraction of the external oblique musculature was quantified using Spike2 software (Cambridge Electronic Designs). Each distension trial lasted 60 seconds, and EMG activity was quantitated in 1-second bins for 20 seconds before distension (baseline), during distention, and 20 seconds after

distention. The increase in total number of recorded counts during distention is defined as the response.

Compound Testing

Stable baseline responses to CRD (80 mm Hg, 20 seconds, 4 minutes apart) was obtained in conscious, unsedated rats before any treatment, followed by oral gavage with 2 doses of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester (12.5 mg/kg and 25 mg/kg) (Time 0). Control animals received vehicle only. At time 16 hours, a pre-zymosan response to distention was measured, followed by second oral doses of experimental compound. The animals were then briefly anesthetized with halothane, and zymosan (1 mL, 25 mg/mL) was instilled into the colon with a gavage needle inserted to a depth of about 7-8 cm, to produce inflammation and enhance the VMR to CRD. Four hours after intracolonic treatment, responses to CRD were quantified as described above.

Results Discussion

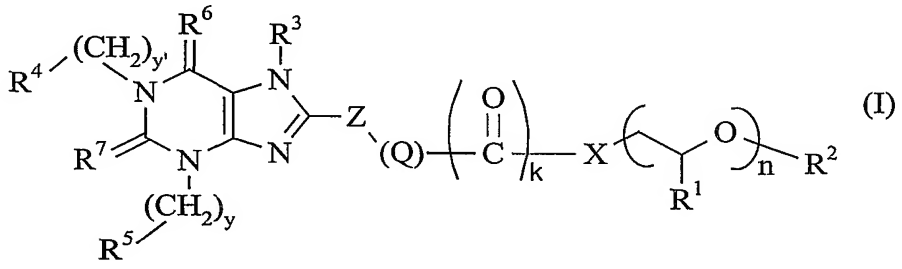
Hyperalgesia is an altered sensory state of increased sensitivity to pain. Visceral hyperalgesia associated with the gastrointestinal tract may arise secondary to infection or inflammation. Such altered visceral sensation, as exemplified by increased sensitivity to colorectal distention, has been observed in patients with functional bowel disorders. Coutinho, Meller, and Gebhart have shown that intracolonic instillation of zymosan, a yeast cell wall derivative which acts as an inflamogen, produces colonic inflammation and enhanced visceromotor responses to colorectal distention as a measurement of response to pain (Ref: Coutinho SV, Meller ST, Gebhart GF. Intracolonic zymosan produces visceral hyperalgesia in the rat that is mediated by spinal NMDA and non-NMDA receptors. Brain Res 1996; 736:7-15).

The results of the study are reported in **Figure 1**. Results from evaluation of (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester in this model show that this compound was

efficacious in decreasing zymosan-induced visceral hypersensitivity to colorectal distention. Both doses (12.5 and 25 mg/kg) of the compound effectively decreased the response to colorectal distention down to baseline levels. Results are expressed as percentage of control, with baseline levels at 100% of control. Increased hypersensitivity is evidenced by increases over 100% of responses to colorectal distention. Overall, these data indicate that (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester is useful for the treatment and prophylaxis of irritable bowel syndrome and functional dyspepsia.

Claims

1. A method for the treatment or prophylaxis of irritable bowel syndrome in an animal, said method comprising administering to said animal a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

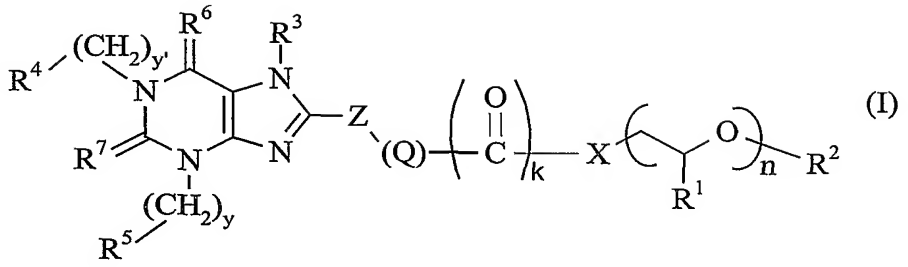
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

2. A method for the treatment or prophylaxis of functional dyspepsia in an animal, said method comprising administering to said animal a therapeutically effective amount of a compound of formula (I):



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

$-N(C_{1-6}alkyl)-$,

$-N(C_{3-8}cycloalkyl)-$,

$-N(C_{1-8}alkyl)(C_{3-8}$ cycloalkyl), and

$-N[(CH_2CH_2O)_m(C_{1-12}$ alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl,

CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof.

3. The method according to claim 1 or 2 wherein the compound of formula (I) is selected from the group consisting of:

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

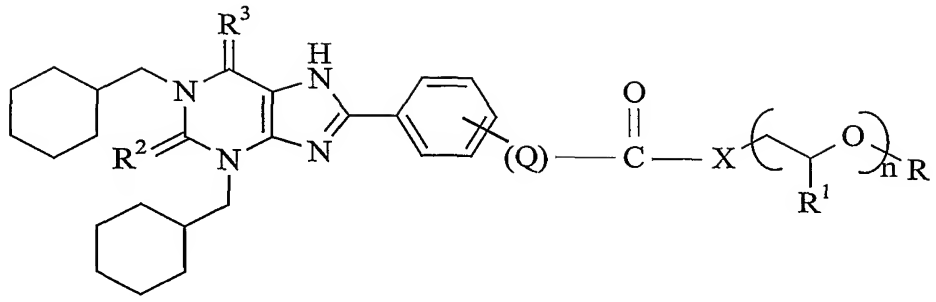
(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

4. The method according to claim 1 or 2, wherein the compound of formula (I) is (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester, or a pharmaceutically acceptable solvate thereof.

5. The method according to claim 1 or 2, wherein the compound of formula (I) is a compound of formula (I-A):



(I-A)

wherein:

X is -O- or -NH-;

Q is selected from the group consisting of $(-CH_2-)_p$, $(-CH=CH-)_p$ and $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

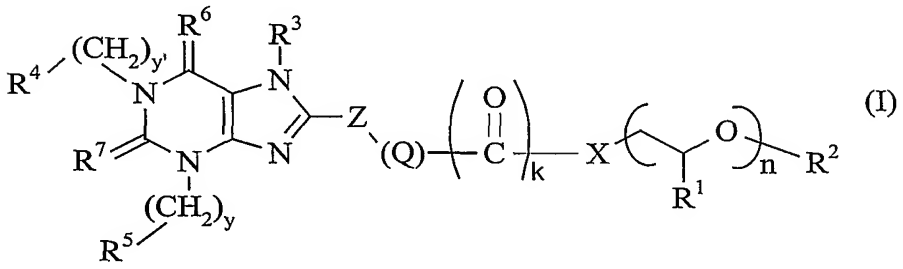
R^2 and R^3 are each independently O or S.

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

6. The use of a compound of formula (I) :



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl), and

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-;

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl–NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

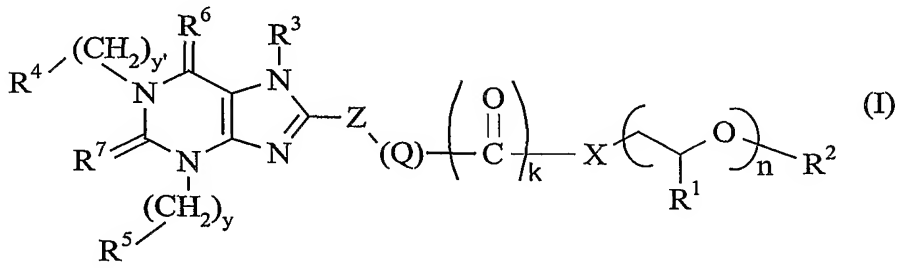
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof, for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

7. The use of a compound of formula (I) :



(I)

wherein:

Z is selected from the group consisting of C_{5-6}cycloalkyl, C_6aryl, substituted C_{5-6}cycloalkyl, substituted C_6aryl, 5- or 6-membered heterocyclic group, substituted 5- or 6-membered heterocyclic group, 5- or 6-membered heteroaryl and substituted 5- or 6-membered heteroaryl;

R^1 is H or methyl;

R^2 is H, C_{1-12}alkyl, aryl, or aralkyl;

k is 0 or 1;

n is an integer 1 to 50;

X is selected from the group consisting of

-O-,

-N(H)-,

-N(C_{1-6}alkyl)-,

-N(C_{3-8}cycloalkyl)-,

-N(C_{1-8}alkyl)(C_{3-8} cycloalkyl),

-N[$(CH_2CH_2O)_m$(C_{1-12} alkyl, aryl, or aralkyl)]-,

m is 0-12;

Q is selected from the group consisting of $(-CH_2)_p$, $(-CH=CH-)_p$, $(-C\equiv C-)_p$, $(-OCH_2-)_p$ and $(-CH_2O-)_p$ where p is 0 to 4;

y and y' are each independently 0 to 10;

R^3 is selected from the group consisting of

H;

straight or branched C_{1-12}alkyl wherein said alkyl may optionally be substituted with a functional group selected from the group consisting of phenyl, -CO-phenyl, CN, -CO(C_{1-3})alkyl, -CO_2(C_{1-3}alkyl), and wherein said C_{1-12}alkyl may optionally have one or more O atoms in the alkyl chain;

straight or branched C_{2-6}alkenyl;

straight or branched C_{2-6}alkynyl; and

-C_{1-3}alkyl-NR^8R^9 wherein R^8 and R^9 are each independently selected from the group consisting of H and C_{1-3}alkyl or R^8 and R^9 together with the N to which they are bonded form a 5- or 6-membered heterocyclic group, optionally containing 1 or 2 other heteroatoms selected from the group consisting of O, N and S;

R^4 and R^5 are each independently selected from the group consisting of

-C_{3-8}cycloalkyl,

-straight or branched C_{1-6}alkyl,

-H,

-straight or branched C_{2-6}alkenyl,

-aryl,

-substituted aryl,

-heterocyclic group,

-substituted heterocyclic group,

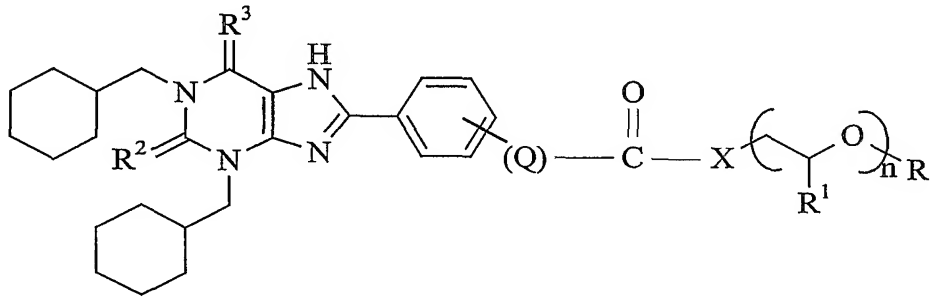
-heteroaryl and

-substituted heteroaryl; and

R^6 and R^7 are each independently O or S;

or a pharmaceutically acceptable solvate thereof, for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

8. The use according to claim 6 or 7, wherein the compound of formula (I) is a compound of formula (I-A)



(I-A)

wherein:

X is -O- or -NH-;

Q is selected from the group consisting of $(-CH_2-)_p$, $(-CH=CH-)_p$ and $(-C\equiv C-)_p$ where p is 0 to 4;

R^1 is H or methyl;

R^2 and R^3 are each independently O or S;

n is an integer 1 to 50; and

R is H or methyl;

or a pharmaceutically acceptable solvate thereof.

9. The use according to claim 6 or 7 wherein the compound of formula (I) is selected from the group consisting of:

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclopropylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-((1-propyl-3-benzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cycloheptylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(phenyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-propyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(bicyclo(2.2.1)hept-2-ylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-cyclohexylmethyl-3-butyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(benzyl)-1,2,3,6-tetrahydro-2-thioxo-6-oxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-(3-cyanobenzyl))-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(3-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bis(2-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1,3-bisphenethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-cyclohexylmethyl-3-methyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-((1-H-3-(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(4-fluorobenzyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol dodecyl Ether Ester;

(E)-4-(1,3-bis(cyclobutylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1-methyl-3-isobutyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-bis(cyclohexyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(cyclopentylmethyl)-1,2,3,6-tetrahydro-6-oxo-2-thioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-bis(2-methyl-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-((1-cyclohexylmethyl-3-propyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)benzoic Acid-N-methyl-Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-oxo-2-phenylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-propynyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo7-(2-oxo-2-methylethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(3-morpholinopropyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-ethyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-ethoxy-2-oxoethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(2-methyl-2-propenyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-(cyanomethyl)-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)phenyl] propionic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-benzyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)benzoic Acid Nonaethylene Glycol Methyl Ether Amide;

1,3-Bis(cyclohexylmethyl)-8-[4-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-3-[5-[1,3-bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1H-purin-8-yl]-2-thienyl]-2-propenoic Acid Nonaethylene Glycol Methyl Ether Ester;

6-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)nicotinic Acid Nonaethylene Glycol Methyl Ether Amide;

(E)-3-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid N-cyclopropylmethyl Nonaethylene Glycol Methyl Ether Amide ;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Hexaethylene Glycol Benzyl Ether Amide;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[(3-Cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-1,7-dimethyl-1H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine Heptaethylene Glycol Methyl Ether;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Heptaethylene Glycol Methyl Ether Hydrochloride;

4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzylamine N-Nonaethylene Glycol Methyl Ether;

1,3-Bis(cyclohexylmethyl)-8-[3-(2,5,8,11,14,17,20,23,26,29-decaoxatriacont-1-yl)phenyl]-3,7-dihydro-1H-purine-2,6-dione;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Heptaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-methyl-1H-purin-8-yl)cinnamic Acid Pentaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-2,3,6,7-tetrahydro-2,6-dioxo-7-propyl-1H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Decaethylene Glycol Methyl Ether Ester;

(E)-4-(1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-3-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]cinnamic Acid Nonaethylene Glycol Methyl Ether Ester;

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid Nonaethylene Glycol Methyl Ether Amide; and

(E)-4-[1,3-Bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl]benzoic acid Nonaethylene Glycol Methyl Ether Ester; and

pharmaceutically acceptable solvates thereof.

10. The use according to any of claims 6, 7 and 8 wherein the compound of formula (I) is (E)-4-(1,3-bis(cyclohexylmethyl)-1,2,3,6-tetrahydro-2,6-dioxo-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester or a pharmaceutically acceptable solvate thereof.

11. A method for the treatment or prophylaxis of irritable bowel syndrome in an animal, said method comprising administering to said animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

12. A method for the treatment or prophylaxis of functional dyspepsia in an animal, said method comprising administering to said animal a therapeutically effective amount of an endothelial cell adhesion molecule inhibitor.

13. The use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of irritable bowel syndrome in an animal.

14. The use of an endothelial cell adhesion molecule inhibitor for the preparation of a medicament for the treatment or prophylaxis of functional dyspepsia in an animal.

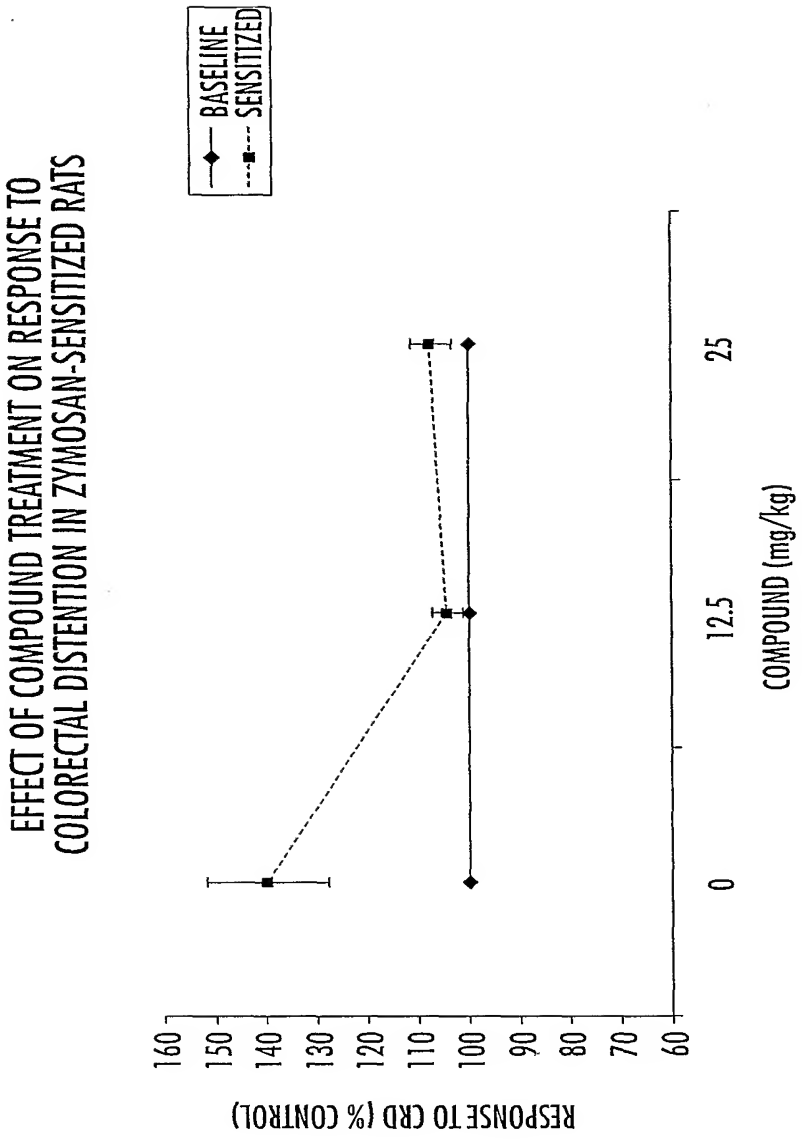

EFFECT OF COMPOUND TREATMENT ON RESPONSE TO COLORECTAL DISTENTION IN ZYMOSAN-SENSITIZED RATS
BASELINE
SENSITIZED
RESPONSE TO CRD (% CONTROL)
160
150
140
130
120
110
100
90
80
70
60
0
12.5
25
COMPOUND (mg/kg)

FIG. 1.